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Iron Chelator in Patients with Sickle Cell Anemia, Comparative Study
طوارد الحديد لمرضى فقر الدم المنجلي ،دراسة مقارنة

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الخلاصة
خلفية البحث :إنّ السببين الرئيسيين لنقلِ الدَم في مرضِ خليةِ الدم المنجلي لتُصحّح فقر الَدم لكي تحسن قابلية نقل الأوكسجين ولمنع حدوث الانسداد الوعائي بتقليل نسبة خضاب الدم المنجلي.االحمل الحديدي سيكون وارد الحصول.
الهدف : إنّ هدف هذه الدراسةِ لمقارنة الأمان وكفاءةِ علاجِ مختلف طوارد الحديد.
المنهجية ؛اثنان و خمسون مريض قسّموا إلى مجموعتين متساويتين، للمعالجةِ بعلاج Deferoxamineالمشترك مع عقار Deferasiro و على Deferasirox لوحده.أجريت الدراسة للفترة من اذار 2012 لغاية نهاية شباط 2013.عملت فحوص الفرتين و وظائف الكبد والكلى كوسائل للمتابعة والمقارنة.
النّتائج : أثبتت كلتا أنظمة العلاج أن لا تأثير مضادً على الوظيفةِ الكبديةِ أَو الكلويةِ .إن درجةَ هبوط الفريتين في مصلِ الدم أعلى جدا بعلاج Deferoxamine_ Deferasirox المشترك.
الاستنتاج : العلاج المشترك Deferoxamine__Deferasirox له تأثير هام على نسبة الفريتين في المصلِ بالمستوى المقبولِ مِن الأمانِ.
التوصيات : العلاج المشترك كَان نظاماً آمنا ممكن استعماله بكفاءة جيدةٍ لمرضى فقر الدم المنجلي ذوي الحملِ الحديدي الزائد.

Abstract
Background: the two main reasons for blood transfusion in sickle cell disease are to correct anemia so that the oxygen-carrying capacity of the blood is improved, and to treat or prevent painful vasoocclusive by lowering the proportion of sickle cell hemoglobin. Iron over load will be evitable.
Aim: The aim of this study is to asses safety and efficiency of different chelation therapy.
Patients and method: Fifty two patients divided in to two equal group, for treatment by combined Deferoxamine-Deferasirox therapy and on Deferasirox alone.
Results: both drug regimens proved to have no adverse effect on hepatic or renal function. The degree of descend of serum ferritin is significantly higher with combined Deferoxamine-Deferasirox therapy.
Conclusion: combined chelating agents have significant effect on serum ferritin, with acceptable level of safety.
Recommendation: combined therapy was safe regime and can be used with good efficacy for patients with iron over load.
Key wards: sickle cell disease. Iron overload. Serum ferritin

INTRODUCTION:

Advances in molecular and cellular biology have broadened our manifestations of sickle cell disease(SCD) can be attributed to vaso-occlusion and chronic hemolysis.[1]the use of blood transfusion in this disease is increasing, and blood transfusion therapy is now considered standard care for primary and secondary stroke prevention in children with SCD.[2]

The use of transfusion therapy in SCD is increasing because of recent evidence indicating its ability to prevent organ injury and improved the outcome of complications[3].

the body has no active mechanism to excrete accumulated iron. Iron over load cause tissue damage such as heart failure, liver disease ,endocrine disturbance which could cause eventual death failure .Transfusion is necessary with the aim of reducing the proportion of hemoglobin S to less than 30% of the total while not raising the total hemoglobin _10 gm/dL. Automated red cell exchange[4,5]

Recent evidence suggests that serial serum ferritin in steady state correlate significantly with liver iron concentration through magmatic resonant imaging(MRI) and can be cost effective readily available tool for iron over load monitoring in SCD particularly in regions with limited resources and high disease burden.

Liver iron content has been accepted as the most accurate quantitative means of determining whole-body iron concentration. However, liver biopsy is not indicated for routine assessment due to its invasive nature. [5].

For many patients with chronic anemia's, regular red blood cell transfusions are lifesaving. However, with each unit of transfused blood, 200–250 mg of iron is transferred to the patient. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over5–10 years) to toxic levels that affect major organs such as the heart and liver.1 This condition, commonly known as iron overload or transfusion hemosiderosis, can cause organ damage anddeath.2 Currently the only way to prevent this is by long-term chelation therapy.[6]

The first oral iron chelator introduced to the US was Deferasirox (DFX), which is additionally licensed in Europe and other regions for the treatment of iron overload. Its long half-life of 11–19hours maintains plasma levels within the therapeutic range over a24-hour period, allowing for a convenient once-daily oral administrationand offering a viable option over Deferoxamine (DFO)and its associated problems with compliance.[7]

Deferoxamine has until now been considered the treatment of choice for patients with chronic iron overload. In recent years multiple different iron chelating regimens were used, which include: monotherapy, combined and alternative sequential regimens. [8]

Deferasirox is an orally activeiron-chelating agent that binds iron in a 2:1 ratio and is primarily excreted in feces. It is given oncedaily as an oral suspension (usually in water or fruitjuice) at a dose of 10–30 mg/kg.47

The ease of administration of Deferasirox (oral) compared with Deferoxamine (infusion) might improve patient adherence to therapy7 and, if effective, may also improve quality and quantity of life.[9]

Compliance with the administration of parental Deferoxamine therapy has proven challenging to all groups of patients with transfusion over load.[10]In recent years multiple different iron chelator regimens were used, which include monotherapy, combined and alternative sequential regimens[11]. The aim of study is to assess the safety of combined Deferoxamine-Deferasirox therapy for patients with sickle cell disease.

PATIENTS AND METHOD:

This prospective comparative study was performed in Najaf thalassemia center, from March 2012,untilend of February 2013patients enrolled was 52 of sickle cell patients. Twenty six were chosen to have (DFX) therapy, randomly by way (3:1) sequence of their files .Hemoglobin level of all patients was maintained between (8.6-9.8gm|dl).starting oral dose was 30\mg |kg day, before breakfast, increased gradually by 5mg|kg|month,till dose of 40 mg|kg|day. Twenty six patients were already on (DFO)therapy on dose of 20 mg|kg|day, subcutaneously infused by special portable device,12 hour a day, five days a week. when they were chosen to enter this study, their therapy changes to combined (DFO) 20mg\kg\day infusion two days per week, and (DFX) in dose of 40 mg\kg\day seven days per week. Written consents was taken from patients or parents who chose combined therapy, and the draw back of each drugs were clarified for all patients in both group. Serum ferritin level of those who

were on DFX alone at the start was(4692-12600mcg|l),while ferritin level of those who chose combined therapy, at the start, was(5268-9035mcg|l). For all patients Cell Blood Count (CBC), serum ferritin by miniuvidus, alanine aminotransferase (ALT), blood urea, serum creatinine and prothrombine time were tested. Patients were excluded if they had a serum creatinine above the upper limit of normal, or if they have positive serological test of hepatitis. After collecting data, statistical analysis was performed by SPSS 16.0.2. Differences were considered significant at PV <0.05

RESULTS

For those patients who chose continuation on combined DFX-DFO therapy median serum ferritin level at the start was6337mcg\l range (5268-9035)l,at the end of first year median ferritin was 4850mcg\l ,rang(4515-8114)and the paired deference was 1480mcg\l,p-value is significant(0.012).(table2).sTwenty six patients who were on DFX alone ,at the point of the end their median serum ferritin decline from 7351mcg\l, range(6326-12600mcg\l) to the level of6379 mcg\l , range(3406-11869)\\ paired deference between the two pints was 982mcg\l, p value is significant (0.0124)(table 1).It is apparent that there washigher and significant descent in serum ferritin for patients on combined therapy- p-value is significant,(1480 versus 982 mcg\l)Median aspartate amino transferase (ALT),and aspartate amino transferase was maintained with in safe level between the reading at the start and at the end of the study(86±16 iu\lat the start and 66±9iu\l at the end for ALT) and (62±12 ---83±8 for ASTiu\l) respectively, without any abnormal surge,(table1).p-value was more than 0.05 for both group. patients on combined therapy, also there was no significant deference in the level of ALT and AST noticed at the end of the study(table2).

Table 1 ;liver enzymes ,renal test changes for patients on Deferasirox alone

Test	Range	Start –mean	End –mean	Range	P value
S F	6326-12600	7351	6379mcg \l	3406-11869	,012
B U	24 – 32	30	26.4	23 -30	NS
S C	0.3 – 0.6	0.42	0.52		NS
ALT	70 – 102	86±16	66±9 IU \ L	57 -75	NS
AST	50 -74	62±12	83±8 IU \ L	75 – 91	NS
PT	12 SEC		13 SEC		NS

Table 1 demonstrate that there was significant reduction in the level of serum ferritin, for patients who chose oral chelation, without significant elevation in liver enzymes and renal function tests.

Table 2 ;variables over one year for patients on combined therapy

Test	Range	Start –mean	End – mean	Range	P value
S F	5269-9035	6337 mcg \ l	4850	4515-8114	0.001
B U	25-34	27.5mg \l	26.5	24-31	NS
S C	0.3 –O,6	0.4 mg \ l	0.5	0.4-0.7	NS
ALT	78-104	91± 8 IU \L	89± 11	75 -131	NS
AST	62- 123	78±11 IU \L	84±13	67- 109	NS
PT		14Sec	13		NS

Table 2 clarified that, combined therapy still maintained safety within acceptable range, with remarkable reduction in level of serum ferritin, with significant variation from decline for those on oral Deferasirox. Renal function test was assessed for time of the study by blood urea and serum creatinine, for both group of patients reading remain much lower than permissible level of safety (table 1). For those who were on combined therapy, also there was no significant deference in the level of ALT noticed at the end of the study (table2). For prothrombine time(PT) and aspartate aminotransferase(AST) in both group all reading were maintained with in permitted levels ,and there was no significant surge noticed

DISCUSSION:

Studies have shown that regular transfusions in children with SCD can significantly reduce the risk forprimary and secondary stroke, hospitalizations, vaso-occlusive events, acute chest syndrome, and growth failure.[12,13]The overall compliance of our patients was very promising , since no one of them escape the treatment program and follow up for the total one year period. Compliance with the administration of parentalDeferoxamine therapy has proven challenging to all groups of patients with transfusion over load[13]Result of our study at the point of the end clarified as shown in table(1))that serum ferritin was decreased by significant proportion (966mcg\l) in those who were on oral DFX this study and result consistent with global new idea about new oral chelator DFX. Deferasirox is effective oral iron chelator with a long half-life, which could be used as monotherapy. It could provide constant gap-free chelation coverage with a single daily dose, and efficient and selective role on organs such as heart and live [17-20]. Deferasirox could produce an acceptable 24 hours iron chelator coverage. However, the efficacy on the high iron

overload is questionable. It could not achieve a negative iron balance even with highest recommended dose, which might cause severe side effects. So, none of iron chelator drugs could provide all therapeutic goals. The iron chelator Deferoxamine (Desferal [DFO, Novar-tis Pharma AG, Basel, Switzerland]) has had a dramatic effect on long-term survival and morbidity of thalassemia patients. It has established an excellent safety andefficacy profile for pediatric patients through several de-cades of clinical use.(14)

Recent evidence indicated thatcontinuous Deferoxamine infusions may reverse iron-induced heart failure. Deferoxamine, however, haspoor oral bioavailability and a short half-life, necessitating administration as an 8- to 12-hour overnight subcutaneous infusion 5 to 7 days per week or as a 24-hourintravenous infusion. Such regimens are extremely burdensome and often lead to poor compliance, particularly in adolescent patients.(16) Those who do not comply with their treatment are usually undergo chelation in-adequately, which has a significant impact on survival. This is especially a concern for iron-overloaded pediatric patients because most will require lifelong chelationtherapy(15)

Combined DFO (20 mg/kg/day, 2days/wk.) and DFX therapy (40 mg/kg/day, 7 days per week) have shown significant and safe decline in mean serum ferritin (6337 mcg\l) to (4850mcg\l) with no clear changes in hepatic or renal function. Combination therapy first practiced in major thalassemia by Anderson et al. They used combination Deferoxamine / Deferiprone and proposed several potential advantages with this regimen (17). Medicines with different properties and mechanisms may access different iron pools. The molecule of Deferasirox is small and can easily enter into cells and is able to transfer iron into plasma for Deferoxamine.(18) In turkey the effectiveness of the alternating use of Deferiprone and Deferoxamine was initially studded, thisstudy serum ferritin decreased significantly. This regimen was associated with minimal adverse effect.(19)

The major serious side effect of this regimen was creatinine rising which occurred in 21% of patients(19).this problem was not encountered in our study, which may be explained by racial difference and small sample in this center. Our study reveal significant reduction of level of serum ferritin In both groups using combined or oral therapy, with maintains of acceptable safety and efficiency, although the rate of reduction was higher in patients on combined Deferoxamine-Deferasirox therapy. This study try to maintained faster and better declined in serum ferritin with maintained of best patients compliance and drug reliability, since we try to reduce the troublesome of subcutaneous injections of DFO together with simplicity with which the oral DFX characteristic(20.21.22).This approach of therapy is a flexible regimen, which would allow the clinicians reduce the nightly Deferoxamine injections and increase the oral dose. The only disadvantage of this regimen is the absence of gap free iron chelator time. Combined regimen was associated with minimal adverse effect as it was showed by insignificant changes in liver enzymes, PT, BU and Serum creatinine.

It has been shown that simultaneous administration of DFO and DFX rapidly reduced systemic and myocardial iron, and provided an excellent control of the toxic labile plasma iron species without an increase in toxicity ,study done to evaluate the safety and efficacy of combined therapy with Deferasirox (DFX, 20-30 mg/kg daily) and Deferoxamine (DFO, 35-50 mg/kg on 3 days/week) in 22 patients with persistent iron overload or organ damage.[22]

Serum ferritin may be unreliable for estimating body iron because vaso-occlusive crises are associated with elevation of serum ferritin. However serum ferritin trends in between quantitative hepatic iron measurements can be useful, provided the serum ferritin tests are always carried out when the patients is in steady state[23]. Our study end with the result that ; although there was significant reduction in serum ferritin observed in all patients who chose both type of therapy , there was no significant side effect ,together it maintained renal function and liver enzymes with in the safe limit, in spite of these promising results there was significant difference in rate and degree of reduction of serum ferritin noticed inpatients on combined therapy.

CONCLUSIONS:

Combined Deferoxamine- deferasiraox therapy proved to be efficient and with insignificant negative effect on renal or hepatic function. The rate of reduction of serum ferritin is higher for patients on Deferoxamine-Deferasirox therapy ,with statistically significant variation.

RECOMMENDATION:

1. For treatments of iron overload in patients with SCD, Deferoxamine-Deferasiraox is safe and convenient with better patients compliance.
2. Larger group of patients need to be restudied for better evaluation of combined Deferoxamine-Deferasirox therapy.

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